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Maternal C^W Alloimmunization

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Abstract

The Winnipeg Rh Laboratory has reviewed its experiences with maternal C^W alloimmunization. From September 24, 1956, to March 31, 1992, 12 women with significant C^W alloimmunization underwent 18 pregnancies. In 3 (4 pregnancies) the antibody, despite its strength, was 'naturally occurring' (i.e. there was no known exposure to C^W-positive red cells). The remaining 9 women (14 pregnancies) had C^W-positive husbands. Two had C^W-negative babies and a third infant, probably C^W negative, was stillborn and macerated at 43 weeks gestation. Eleven babies were C^W positive and had hemolytic disease of the newborn (HDN), with antiglobulin-positive red cells. Five did not require treatment; 2 needed phototherapy only, and 4 (born between 1956 and 1963) required exchange transfusions. No anti-C^W screening was carried out until 1977; thereafter it was sporadic, 11 of 51 screening red cells being C^W positive in the 39-month period ending March 31st, 1992. From November 1, 1977, to March 31, 1992, 24 women (30 pregnancies, 31 conceptuses) with insignificant anti-C^W alloantibodies were identified. Extrapolating these figures to the entire period from September 24, 1956, to March 31, 1992, we estimate that at least 430 women (at least 573 pregnancies) were C^W alloimmunized, most of the antibodies being 'naturally occurring'. Only 2% of the conceptuses were C^W positive and affected; none were severely affected. Anti-C^W is relatively common, occurring in about 1 pregnant Manitoban woman in 1,100. On very rare occasions (11 times in Manitoba in 36 years and 5 months) anti-C^W HDN occurs which, although not severe, may end in kernicterus with brain damage or neonatal death unless it is detected promptly and treated appropriately.

Introduction

The red cell surface antigen C^W, attributable to an allele C^W at the Cc locus of the Rh system, occurs in about 2% of Caucasians (5–7% of Lapps, Latvians, and Finns). Anti-C^W was first described by Callender et al. [1] in a multiply transfused patient with systemic lupus erythematosus. Since Lawler and van Loghem's report [2] of anti-C^W in a nontransfused woman who had 3 infants, all of whom in retrospect died of kernicterus, there have been very few reports of C^W hemolytic disease of the newborn (HDN) and none to our knowledge of hydrops fetalis or fetal death due to C^W alloimmunization.

The birth, in Manitoba in March 1992, of a baby with mild C^W HDN stimulated us to review our experience with C^W alloimmunization and C^W HDN. We also reviewed the literature pertaining to C^W alloimmunization and C^W HDN.

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Materials and Methods

Since its founding in 1944, the Winnipeg Rh Laboratory has been responsible for blood grouping and antibody screening of all pregnant women in the province of Manitoba, population 1 million. Numbers of pregnancies in the earlier years were in excess of 20,000 annually, dropping to about 17,000 annually in the past 20 years. Screening of Rh-positive pregnant women has been routine since 1967. However, the use of a C^w-positive screening red cell (with the exception of one C^w-positive red cell in 1951) was not introduced until 1977. Since then the use of such a cell has been sporadic. From January 1, 1989, to March 31, 1992, 11 of 51 screening cells were C^w positive. When the screening cell was not C^w positive, the Rh Laboratory would be made aware of babies with clinical C^w HDN, since it does routine cord blood direct antiglobulin testing (DAT) of babies delivered at the main tertiary level centre (Health Sciences Centre) and is the laboratory responsible for investigation and clinical management of all newborn infants with HDN (and severe hyperbilirubinemia) in Manitoba.

The Rh Laboratory records which date back to 1944 were surveyed for all instances of maternal C^w alloimmunization and C^w HDN. The first documented case of maternal C^w alloimmunization was discovered in 1951 [3] and the first case of C^w HDN occurred on September 24th, 1956. Since anti-C^w is usually found in combination with anti-C, only those pregnancies wherein anti-C^w was the only antibody or was of much higher titre than the anti-C were included in the survey. Wherever possible, the C^w status of the putative father, history of blood transfusion, C^w status of the conceptus, and pregnancy outcome were determined.

The literature pertaining to C^w alloimmunization and C^w HDN was surveyed from 1947 to February 1992 (quarterly cumulative Index Medicus 1947–1950, current list of medical literature 1950–1959, cumulated Index Medicus 1960 to February 1992). Case reports of C^w alloimmunization and C^w HDN and atypical blood group alloimmunization surveys were reviewed.

Results

Our survey of C^w alloimmunization and C^w HDN in Manitoba is set out in tables 1 and 2. The data are subdivided into: serologically significant anti-C^w, strongly reactive by a timed capillary indirect antiglobulin technique (IAT) [4] within 1–3 min (table 1), and serologically insignificant anti-C^w, detectable by enzyme and weakly in more than 6 min or not at all by a timed capillary IAT (table 2). The degree of fetal-neonatal HDN is classified as follows: category 1 (C1) red cells DAT positive not requiring treatment; category 2A (C2A) red cells DAT positive requiring phototherapy only; category 2B (C2B) requiring exchange transfusion; category 3 (C3) severely affected, cord hemoglobin between 60 and 90 g/l or serum indirect bilirubin ≥ 105 μmol/l (≥ 6 mg/dl) requiring

Table 1. Significant C^w alloimmunization Manitoba, Winnipeg Rh Laboratory, September 24, 1956, to March 31, 1992

Women (pregnancies)	Fathers			Transfused			Titre range IAT	Naturally occurring (pregnancies)	Pregnancy outcome			Category				
	C^w-	C^w+	$C^w??$	yes	no	??			SB	C^w-	C^w+	1	2A	2B	3	4
12 (18)	3	9	1[1]	3	6	3	4–256	3 (4)	1[1]	6	11	5	2	4	0	0

C^w+ = C^w Positive; C^w- = C^w negative; $C^w??$ = C^w status of father unknown; SB = stillbirth.

[1] 43 weeks gestation, postmature stillbirth, father C^w unknown, not father of prior C^w+ve, category 2B baby, 99% likelihood fetus C^w-ve.

Table 2. Insignificant[1] C^w alloimmunization Manitoba, Winnipeg Rh Laboratory, January, 1977, to March 31, 1992[2]

Women[3] (pregnancies)	Father			Transfused			Naturally occurring (pregnancies)	Pregnancy outcome		
	C^w-	C^w+	$C^w??$	yes	no	??		abortion	C^w-	C^w+
24 (30)[2]	8	1	15	3	8	13	24 (30)	9	22[4]	0

C^w- = C^w negative; C^w+ = C^w positive; $C^w??$ = C^w status unknown.

[1] Anti-C^w detected by enzyme technique or very weakly > 6 min by IAT.

[2] 11 of 51 screening red cells C^w+ve, January 1, 1989, to March 31, 1992, when 11 C^w-alloimmunized pregnant women identified.

[3] C^w-alloimmunized woman, discovered in 1951 [3], not included.

[4] One set of twins.

prompt exchange transfusion; category 4 (C4) very severely affected, cord hemoglobin < 60 g/l or hydropic or stillborn.

Twelve women (18 pregnancies) had significant anti-C^w. Anti-C^w IAT titres ranged from 4 to 256 (positive in less than 1 min to positive within 3 min by timed capillary IAT). Despite the presence of significant anti-C^w in 3 of the 12 women, the anti-C^w must have been 'naturally occurring' since they gave no history of C^w exposure (no transfusions), had C^w-negative husbands and delivered 4 C^w-negative babies.

The remaining 9 women (10 husbands, 14 pregnancies) produced 2 C^w-negative babies and 1 macerated stillbirth at 43 weaks gestation probably due to postmaturity with a 99% probability of being C^w negative, being fathered by a second husband of unknown C^w status (98% probability C^w negative), the first husband, C^w positive, having fathered a baby with category 2B C^w HDN. Eleven babies were C^w positive, DAT positive: 5 category 1, 2 category 2A, 4 category 2B (all born between 1956 and 1963), none category 3 or category 4. Of these 9 women, 3 gave a history of transfusion (1 of 3 had a massive C^w-positive fetomaternal transplacental hemorrhage), 3 were not transfused, and in 3 the transfusion history was unknown.

From 1977 to March 31, 1992, when anti-C^w screening was sporadic, 24 women (30 pregnancies, 31 conceptuses; table 2) were identified as having weak, insignificant antiC^w. They delivered 22 C^w-negative babies, no C^w-positive babies, and had 9 abortions (spontaneous or induced). Eight had C^w-negative husbands, 1 a C^w-positive husband; in 15 the C^w status of the husband was unknown. Three had a history of blood transfusions, 8 had no transfusions, and in 13 the transfusion history was unknown.

From January 1, 1989, to March 31, 1992, when 11 of 51 panels of screening red cells were C^w positive, 11 C^w-alloimmunized women were identified. If all screening cells in the 39-month period had been C^w positive, we estimate that 51 C^w-alloimmunized women would have been detected, a C^w alloimmunization rate of approximately 1 per 1,100 pregnancies. Extrapolating these numbers to the entire period, September 24, 1956, to March 31, 1992, and disregarding the increased numbers of pregnancies prior to 1970, we calculated that there were at least 430 C^w-alloimmunized women who had at least 573 pregnancies. In only 11 of them (2%) were the conceptuses C^w positive and affected with HDN.

Table 3. C^w hemolytic disease case reports

Authors	Date	Titre IAT	Transfused	Disease category	Outcome
Lawler and van Loghem [2]	1947	–	No	C2 (×3)	3NND K1
Sacks et al. [5]	1958	16	??	C1	AW
Anderson and Fenton [6]	1963	32	Yes	C1	AW
Geiger [7]	1959	–	Yes	C2B	AW
Mogilner et al. [8]	1982	256	No	C2B	AW
Hughes et al. [9]	1983	128	No	C2B	AW
Musialowicz and Szmigiel [10]	1980	4	??	C2B	AW

NND K1 = Neonatal death from kernicterus (1941, 1944, 1947); AW = alive and well.

Discussion

In a review of C^w case reports in the literature (table 3), we were able to find only 7 reports of C^w HDN. Lawler and van Loghem [2], in the first report of C^w HDN, reported a nontransfused woman, determined in 1947 to be C^w negative with anti-C^w, who had 3 infants (1941, 1944, 1947) who developed 'icterus gravis' and died in the neonatal period, in retrospect, undoubtedly from kernicterus. The 6 other case reports of C^w HDN (infants' red cells DAT positive) include 2 category 1 infants [6, 7] not requiring treatment, maternal anti-C^w IAT 16 and 32 and 4 category 2B infants [7–10] requiring either exchange transfusions (2) or multiple nonexchange transfusions (2), maternal anti-C^w IAT 4–256. Two women had been transfused in the past, 3 had not been transfused and in 2, transfusion history was not reported.

Several surveys of non-Rh(D) maternal alloimmunization (table 4) report no C^w alloimmunization [11–13] whereas others report 2–17 (total 36) instances of C^w alloimmunization [14–17], an incidence of between 1 in 2,400 and 1 in 10,750. Either nothing is stated regarding the presence and severity of HDN [14, 15] (21 instances), or the anti-C^w produced no HDN [16, 17] (15 instances).

Our survey reveals that C^w alloimmunization is not uncommon (1 in 1,100 pregnancies). The incidence reported elsewhere (from 0 in 72,138 to 1 in 2,400) undoubtedly represents underreporting due to absence or only sporadic use of a C^w-positive screening red cell. Although C^w alloimmunization is not rare, significant C^w HDN is ex-

Table 4. Maternal anti-C^w in atypical antibody surveys

Authors	Date	Number of women screened	Number with anti-C^w	Incidence of anti.C^w	Outcome	
					C^w HDN	no C^w HDN
Queenan et al. [11]	1969	18,378	0[1]	0/18,378	0	0
Pepperel et al. [12]	1977	72,138	0[1]	0/72,138	0	0
Solola et al. [13]	1983	6,025	0[1]	0/6,025	0	0
Polesky [14]	1967	43,000	5[2]	1/10,750	?	?
Beal [15]	1979	41,078	17[2]	1/2,400	?	?
Hardy and Napier [16]	1981	380,790	13[2]	1/3,000	0	13
Zuliani et al. [17]	1983	9,525	2[2]	1/4,760	0	2

? = Numbers of babies with and without C^w HDN not known.
1 C^w+ screening cell probably not used.
2 C^w+ screening cell probably used sporadically.

tremely so, occurring, we estimate, in only 2% of C^w-alloimmunized pregnancies.

It would appear that the majority of maternal C^w alloimmunization is very weak in nature, 98% of such antibodies being insignificant and of no clinical importance. The majority of anti-C^wantibodies, including some of significant strength (3 of 12 in our series), originate in women with no C^w-positive red cell exposure (no blood transfusions and C^w-negative husbands) and must be considered to be 'naturally occurring'. Chown and Lewis [3] discovered, in 1951, anti-C^w in a pregnant woman 'in the absence of known stimulation' (no history of blood transfusion, the husband and 4 children all C^w negative). Kornstad et al. [18] also report 2 examples of probably 'naturally occurring anti-C^w'.

C^w HDN, when it occurs, is only of mild to moderate severity. The only deaths caused by C^w HDN are the 3 neonatal deaths from kernicterus reported by Lawler and van Loghem [1], in babies born in 1941, 1944, and 1947, prior to or just at the beginning of the exchange transfusion era. They would probably have survived intact had exchange transfusions been available and carried out. With these exceptions, all other described cases (n = 31) have been category 2 or less HDN. We could find no reports of C^w HDN so severe that early induced delivery was required or in which severe anemia (hemoglobin < 60 g/l) such as hydrops fetalis, or stillbirth due to HDN occurred, and there were no such cases in our series. Nevertheless, unless C^w HDN is diagnosed promptly when it occurs and is treated appropriately, there is a significant hazard of dangerous hyperbilirubinemia with risk of kernicterus.

Because of the relative frequency of C^w alloimmunization and the finding that the great majority of such examples are insignificant and 'naturally occurring', only about 2% of the babies born of C^w-alloimmunized mothers having HDN and only half of these (1% overall) requiring exchange transfusion and/or phototherapy, it can be argued that routine screening of all pregnant women for C^w alloimmunization leads to a great deal of antibody specificity testing which is time consuming, unnecessary, and not cost effective.

From this study it appears that even when C^w antibody titres are as high as 256 by IAT in our series and in the case reports reviewed, the degree of HDN is not more than category 2. Therefore, even when C^w alloimmunization has been detected, invasive investigative measures such as amniotic fluid spectrophotometry and/or cord blood sampling are not indicated.

Routine direct antiglobulin testing of cord blood promptly after delivery will identify babies with C^w HDN who may require treatment. Failing routine cord blood testing, which we strongly recommend, rapid investigation of any newborn baby who develops significant anemia or hyperbilirubinemia in the newborn period, will allow appropriate management of the rare infant with C^w HDN.

Summary

Anti-C^w alloimmunization, although not uncommon, rarely produces significant HDN. When C^w HDN occurs, it has never been observed to cause hydrops fetalis, fetal death, or severe anemia. On 3 occasions, C^w HDN in the past has caused kernicterus and in the present may place an affected newborn at risk. Routine cord blood DAT or prompt investigation of babies in the newborn nursery who are hyperbilirubinemic or anemic due to C^w HDN will allow diagnosis and appropriate management (exchange transfusion and/or phototherapy) before damage occurs.

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